General

Guideline Title

Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline.

Bibliographic Source(s)

Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML, Endocrine Society. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Jun;96(6):1587-609. [216 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: The Endocrine Society. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. Chevy Chase (MD): Endocrine Society; 2006. 33 p.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (+OOO, ++OO, +++O, and ++++); the strength of the recommendation (1 or 2); and the difference between a "recommendation" and a "suggestion" are provided at the end of the "Major Recommendations" field.

Definition of Growth Hormone Deficiency (GHD) in Adults

The Task Force recommends that patients with childhood-onset GHD who are candidates for growth hormone (GH) therapy after achievement of adult height be retested for GHD as adults unless they have known mutations, embryopathic lesions causing multiple hormone deficits, or irreversible structural lesions/damage (1|++++).

The Task Force recommends that adult patients with structural hypothalamic/pituitary disease, surgery or irradiation in these areas, head trauma, or evidence of other pituitary hormone deficiencies be considered for evaluation for acquired GHD (1|++++).

Idiopathic GHD in adults is very rare, and stringent criteria are necessary to make this diagnosis. Because in the absence of suggestive clinical circumstances there is a significant false-positive error rate in the response to a single GH stimulation test, the Task Force suggests the use of two tests before making this diagnosis. The presence of a low insulin-like growth factor I (IGF-I) also increases the likelihood that this diagnosis is correct (2|+OOO).

Diagnosis of GHD

The Task Force recommends that the insulin tolerance test (ITT) and the growth-hormone-releasing hormone (GHRH)-arginine test have sufficient

sensitivity and specificity to establish the diagnosis of GHD. However, in those with clearly established recent (within 10 years) hypothalamic causes of suspected GHD, e.g. irradiation, testing with growth-hormone-releasing hormone-arginine may be misleading (1|++++).

The Task Force suggests that when GHRH is not available and performance of an insulin tolerance test (ITT) is either contraindicated or not practical in a given patient, the glucagon stimulation test can be used to diagnose GHD (2|++OO).

The Task Force recommends that because of the irreversible nature of the cause of the GHD in children with structural lesions with multiple hormone deficiencies and those with proven genetic causes, a low IGF-I level at least 1 month off GH therapy is sufficient documentation of persistent GHD without additional provocative testing (1|+++O).

The Task Force recommends that a normal IGF-I level does not exclude the diagnosis of GHD but makes provocative testing mandatory to making the diagnosis of GHD (1|++++). However, a low IGF-I level, in the absence of catabolic conditions such as poorly controlled diabetes, liver disease, and oral estrogen therapy, is strong evidence for significant GHD and may be useful in identifying patients who may benefit from treatment and therefore require GH stimulation testing (1|++OO).

The Task Force recommends that the presence of deficiencies in three or more pituitary axes strongly suggests the presence of GHD, and in this context, provocative testing is optional (1|+++O).

Consequences of GHD and Benefits of Treatment with GH

The Task Force recommends that GH therapy of GH-deficient adults offers significant clinical benefits in body composition and exercise capacity (1|+++O).

The Task Force suggests that GH therapy of GH-deficient adults offers significant clinical benefits in skeletal integrity (2|++OO).

The Task Force recommends after documentation of persistent GHD that GH therapy be continued after completion of adult height to obtain full skeletal/muscle maturation during the transition period (1|++OO).

The Task Force suggests that GH therapy of GH-deficient adults improves several cardiovascular surrogate outcomes, including endothelial function, inflammatory cardiovascular biomarkers, lipoprotein metabolism, carotid intima-media thickness (IMT), and aspects of myocardial function, but tends to increase insulin resistance (2|++OO).

The Task Force suggests that, although mortality is increased in patients with hypopituitarism and GHD has been implicated in this, GH has not yet been shown to improve mortality (2|+OOO).

The Task Force suggests that GH therapy of GH-deficient adults improves the quality of life of most patients (2|++OO).

Side Effects and Risks Associated with GH Therapy

The Task Force recommends that treatment is contraindicated in the presence of an active malignancy (1|+OOO).

The Task Force recommends that GH treatment in patients with diabetes mellitus may require adjustments in antidiabetic medications (1|+++O).

The Task Force suggests that thyroid and adrenal function be monitored during GH therapy of adults with GHD (2|++OO).

Treatment Regimens

The Task Force recommends that GH-dosing regimens be individualized rather than weight-based and start with low doses and be titrated according to clinical response, side effects, and IGF-I levels (1|++++).

The Task Force recommends that GH dosing take gender, estrogen status, and age into consideration (1|++++).

The Task Force suggests that during GH treatment, patients be monitored at 1- to 2-month intervals during dose titration and semiannually thereafter with a clinical assessment and an evaluation for adverse effects, IGF-I levels, and other parameters of GH response (2|++OO).

Definitions:

Quality of Evidence

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

Strength of Recommendation

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Adult growth hormone deficiency

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Endocrinology

Intended Users

Physicians

Guideline Objective(s)

- To update The Endocrine Society Clinical Practice Guideline on Evaluation and Treatment of Adult Growth Hormone Deficiency (GHD) previously published in 2006
- To summarize information regarding adult GHD (AGHD), including information published since the previous guideline

Target Population

Adult patients with growth hormone deficiency

Interventions and Practices Considered

Diagnosis/Evaluation

1. Retesting adult patients who were diagnosed with childhood-onset growth hormone deficiency (GHD)
2. Evaluation for acquired GHD
3. Insulin tolerance test (ITT)
4. Growth hormone releasing hormone (GHRH)-arginine test
5. Insulin-like growth factor-I (IGF-I) level
6. Glucagon stimulation test
7. Use of two diagnostic tests before making diagnosis of idiopathic GHD

Treatment with Growth Hormone (GH)

1. Dosing
    - Weight-based vs. individualized
    - Consideration of age, sex, estrogen status
    - Titration according to clinical response, side effects, and IGF-I levels
2. Monitoring
    - Appropriate monitoring intervals
    - Lipid profile
    - Fasting glucose
    - Bone density
    - Adrenal and thyroid function
    - Quality of life
    - Assessment of side effects

Major Outcomes Considered

- Accuracy (sensitivity, specificity) of diagnostic tests for growth hormone (GH) deficiency
- Response to GH treatment in terms of body composition, exercise capacity, skeletal integrity, cardiovascular risk factors, quality of life, and mortality in patients with hypopituitarism
- Side effects and risks of GH treatment

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A systematic review of the literature was commissioned by The Endocrine Society to evaluate the treatment effects of dopamine agonists in patients with adult growth hormone deficiency (see the "Availability of Companion Documents" field).

Data Sources: MEDLINE, EMBASE, Cochrane CENTRAL, Web of Science and Scopus were searched through September 2009. Review of reference lists and contact with experts further identified candidate studies. See the systematic review (see the "Availability of Companion Documents" field) for specific search terms.

Study Selection: Reviewers, working independently and in duplicate, determined study eligibility.

Number of Source Documents

24 studies were included in the analysis.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

A systematic review of the literature was commissioned by The Endocrine Society to evaluate the treatment effects of dopamine agonists in patients with adult growth hormone deficiency (see the "Availability of Companion Documents" field).

Data Synthesis: From each study, reviewers estimated the relative risk (or risk ratio, RR) and 95% confidence interval (CI) for dichotomous outcomes and weighted difference in means (WMD) and 95% CI for continuous outcome. Data were pooled using the random effects model and heterogeneity assessed using the I squared statistic. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to evaluate the quality of evidence.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The Task Force consisted of a chair, selected by the Clinical Guidelines Subcommittee of The Endocrine Society, four additional experts, a methodologist, and a medical writer.

Consensus was guided by systematic reviews of evidence and discussions through a series of conference calls and e-mails. An initial draft was prepared by the Task Force, with the help of a medical writer, and reviewed and commented on by members of The Endocrine Society. A second draft was reviewed and approved by The Endocrine Society Council. At each stage of review, the Task Force received written comments and incorporated substantive changes.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendation

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

An initial draft was reviewed and commented on by members of The Endocrine Society. A second draft was reviewed and approved by The Endocrine Society Council. At each stage of review, the Task Force received written comments and incorporated substantive changes.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is specifically stated for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Accurate diagnosis of growth hormone deficiency (GHD)
- Growth hormone (GH) therapy offers benefits in body composition, exercise capacity, skeletal integrity, and quality of life measures and is most likely to benefit those patients who have more severe growth hormone deficiency.
- The guideline developers suggest that GH therapy of GH-deficient adults improves several cardiovascular surrogate outcomes, including endothelial function, inflammatory cardiovascular biomarkers, lipoprotein metabolism, carotid intima-media thickness (IMT), and aspects of myocardial function.

Potential Harms

- In the absence of suggestive clinical circumstances there is a significant false-positive error rate in the response to a single growth hormone (GH) stimulation test.
- The insulin tolerance test (ITT), which has been considered the most extensively validated "gold standard" test, may carry increased risk in patients with seizure disorders or cardiovascular disease and requires constant monitoring even in healthy adults, although it is quite safe in experienced hands.
- Higher doses of GH can cause peripheral edema in some circumstances.
- GH therapy of GH-deficient adults tends to increase insulin resistance.
- GH therapy of adults with growth hormone deficiency (GHD) has generally been regarded as being quite safe, although concerns remain regarding the potential for cancer risk and tumor regrowth. Although GH treatment decreased insulin sensitivity, the worsening of glycemic control has in general been minimal or transient.
- GH treatment in patients with diabetes mellitus may require adjustments in antidiabetic medications.
- The most common side effects of GH therapy, occurring in 5%–18% of patients, are related to fluid retention and include paresthesias, joint stiffness, peripheral edema, arthralgias, and myalgias. Carpal tunnel syndrome occurs in approximately 2% of treated adult GHD patients.

Adult patients who are older, heavier, or female are more prone to develop these complications. Most of these adverse reactions improve with dose reduction. Increased blood pressure is seen when fluid retention occurs, but this problem can be avoided with appropriate dosing.
- Retinopathy is an extremely rare complication of GH therapy.

Contraindications

Contraindications

Growth hormone treatment is contraindicated in the presence of an active malignancy.

Qualifying Statements

Qualifying Statements

- Clinical Practice Guidelines are developed to be of assistance to endocrinologists and other health care professionals by providing guidance and recommendations for particular areas of practice. The Guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The Guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The Guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of health care providers and each patient's individual circumstances.
- The Endocrine Society makes no warranty, express or implied, regarding the Guidelines and specifically excludes any warranties of merchantability and fitness for a particular use or purpose. The Society shall not be liable for direct, indirect, special, incidental, or consequential damages related to the use of the information contained herein.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Identifying Information and Availability

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2006 (revised 2011 Jun)

Guideline Developer(s)

The Endocrine Society - Professional Association

Source(s) of Funding

The Endocrine Society

The Task Force received no corporate funding or remuneration.

Guideline Committee

Evaluation and Treatment of Adult Growth Hormone Deficiency Task Force

Composition of Group That Authored the Guideline

Task Force Members: Mark E. Molitch (*Chair*); David R. Clemmons; Saul Malozowski; George R. Merriam; Mary Lee Vance

Financial Disclosures/Conflicts of Interest

Mark E. Molitch, M.D. (chair)—Financial or Business/Organizational Interests: Eli Lilly, Co., American Diabetes Association, American College of Physicians, Pituitary Society, Sanofi Aventis, Ipsen, Corcept; Significant Financial Interest or Leadership Position: none declared.

David R. Clemmons, M.D.—Financial or Business/Organizational Interests: Pfizer, Inc., Genentech, Inc., Lilly Inc., Ipsen Inc.; Significant Financial Interest or Leadership Position: none declared.

Saul Malozowski, M.D.—Financial or Business/Organizational Interests: none declared; Significant Financial Interest or Leadership Position: none declared.

George R. Merriam, M.D.— Financial or Business/Organizational Interests: America Neuroendocrine Society, National Institutes of Health, Washington State Health Department; Significant Financial Interest or Leadership Position: Novo Nordisk, Inc., Eli Lilly, Co., American Neuroendocrine Society.

Mary Lee Vance, M.D.—Financial or Business/Organizational Interests: Novartis Pharmaceuticals, Ipsen; Significant Financial Interest or Leadership Position: none declared.

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from The Endocrine Society Web site .

Print copies: Available from The Endocrine Society; Phone: (301) 941.0210; Email: Societyservices@endo-society.org.

Availability of Companion Documents

The following are available:

- Hazem A, Elamin MB, Malaga G, Bancos I, Prevost Y, Zeballos-Palacios C, Velasquez ER, Erwin PJ, Natt N, Montori VM, Murad MH. The accuracy of diagnostic tests for GH deficiency in adults: a systematic review and meta-analysis. Eur J Endocrinol. 2011 Dec;165(6):841-9. Epub 2011 Aug 19. Electronic copies: Available from the European Journal of Endocrinology Web site .
- Hazem A, Elamin MB, Bancos I, Malaga G, Prutsky G, Domecq JP, Elraiyah TA, Abu Elnour NO, Prevost Y, Almandoz JP, Zeballos-Palacios C, Velasquez ER, Erwin PJ, Natt N, Montori VM, Murad MH. Body composition and quality of life in adults treated with GH therapy: a systematic review and meta-analysis. Eur J Endocrinol. 2012 Jan;166(1):13-20. Epub 2011 Aug 24. Available from the European Journal of Endocrinology Web site .

Print copies: Available from The Endocrine Society, Phone: (301) 941.0210; Email: Societyservices@endo-society.org.

In addition, a version of the guideline including a continuing medical education (CME) activity is available for purchase from The Endocrine Society Web site .

Patient Resources

The following is available:

- Patient guide to growth hormone deficiency in adults. The Hormone Foundation. 2011 Jun. 2 p. Electronic copies: Available from The Hormone Foundation Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

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